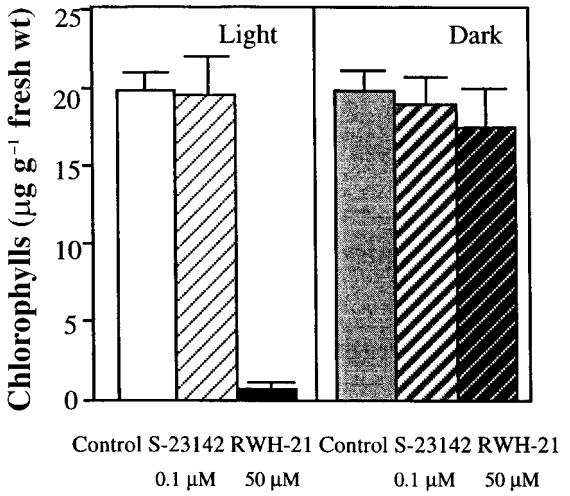

Figure 4. Bleaching activity of RWH-21 against YZI-1S cells. DPE-resistant tobacco cells (YZI-1S) were cultured in the presence of RWH-21 (50 μM) and S-23142 (1 μM), separately. Cell culture conditions are the same as shown in Fig 2.

result is in accordance with our earlier observation that RWH-21 has a mode of action different from that of DPEs.[3]

Our data indicate that compounds inducing the accumulation of 13^2-hydroxychlorophyll *a* in plant tissues could exhibit photo-bleaching herbicidal action. Thus RWH-21 could be a new lead for herbicides, and further investigation on the mode of action of RWH-21 could find a new target site of herbicides.

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Molecular shape similarity between cyclic imides and protoporphyrinogen IX

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Abstract: Comparisons using computational techniques, of shapes and bond angles of compounds which act as protoporphyrinogen IX oxidase (protox) inhibitors indicate structural similarities between the different compounds. Experiments show that cyclic imides and diphenyl ethers both inhibit protox, but have different binding sites.

Keywords: peroxidising herbicides; cyclic imides; protoporphyrinogen IX oxidase; shape similarity index

The peroxidizing compounds shown in Tables 1 and 2, which can, in a broad sense, be considered as cyclic imides – *N*-aryl-3,4,5,6-tetrahydrophthalimides (**2–11**), 4-aryl-1,2-tetramethylene-1,2,4-triazolidines (**12–16**), 5-aryl-3,4-tetramethylene-1,3,4-thiadiazolidines (**17–21**), 3-aryl-1,5-tetramethylene-hydantoins (**22**, **23**), 3-aryl-5-isopropylidene-1,3-oxazolidine-2,4-diones (**24–26**) – and peroxidizing diphenyl ethers (**27–31**) – inhibit chlorophyll biosynthesis and lead to destruction of cellular components with ethane evolution.[1,2] The target enzyme of peroxidizing compounds is protoporphyrinogen IX oxidase (protox, EC 1.3.3.4), and these compounds interact competitively with the substrate, protoporphyrinogen IX (protogen). To assess the steric similarity between peroxidizing compounds and protogen, the most stable molecular structures of some cyclic imides, diphenyl ethers and protogen were calculated and optimized by MOPAC with MNDO-PM3 parameterizations and their steric properties were compared by computational techniques.[3]

An energy-minimum conformation of protogen is shown in Fig 1 and the torsion angle of the pyrrole rings in this conformation are listed in Table 3.

For the most stable conformation of cyclic imides, the torsion angle between the imide moiety and benzene ring was approx. 240–270°, so that the conformers with the torsion angle of 255° were used in the studies of superimposition and molecular similarity as a first approximation.

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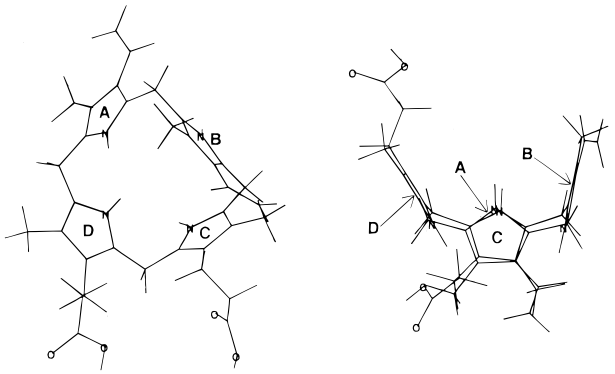


Figure 1. Three-dimensional structure of an energy-minimum conformation of protoporphyrinogen IX. The nitrogens in the A and C rings are located on the opposite side of the 'plane' defined by four -CH_2- bridges towards the B and D rings. The vinyl groups of A and B rings are in *S*-trans and *S*-cis conformations, respectively, with respect to the configuration of double bonds of the vinyl groups and pyrrole rings.

Applying superimposition of protogen and cyclic imides, it was assumed that cyclic imides mimic a part of the protogen molecule in the inhibition process of protox, because the protox molecule is much larger than the cyclic imide molecule. An active peroxidizer, **4** (Table 1), was superimposed with a substructural component of the most stable conformer of protogen by using a computer graphics technique. The benzene ring and the imide moiety of **4** superimposed closely upon the C and D rings of protogen, respectively. In this superimposed model, the 2-ethoxycarbonyl group on the C ring corresponded to the 3-propargyloxy group of **4**, whereas the same substituent on the D ring did not fit any part of **4**. The maximum lengths of the whole molecule of the compound and the 3-propargyloxy group are 11.54 Å and 5.21 Å, respectively, which correspond to the diameter of protogen (10.85 Å) and the length of the 2-ethoxycarbonyl group (5.61 Å). These results suggest that herbicidal cyclic imides mimic the C and D rings of protogen at the reaction site of protox with respect to steric properties.

Based on the results of the superimposition study, we set up a hypothetical protogen substructure containing the C and D rings only, in which the coordinates of each atom in the most stable conformation of protogen were retained, and the methylene bridges toward the A and B rings were replaced by methyl groups. The molecular shape similarity between this model molecule of 'half-protogen' and each of the cyclic imides was quantified by the shape similarity index defined by the equation:[4]

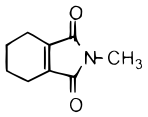
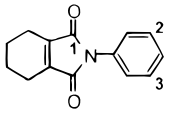
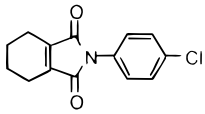
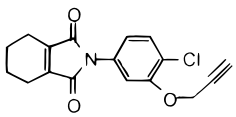
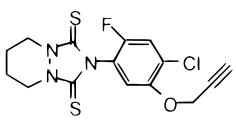
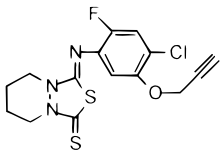
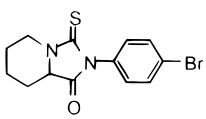
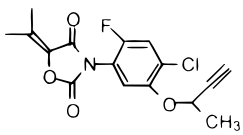
$$S = C/(T_I^* T_{II})^{1/2} \quad (1)$$

In this equation, T_I and T_{II} are the volumes of the molecules I and II, respectively, and C is the common volume shared by the two molecules when they are superimposed. The index S takes a value in the range from 0 to 1, with $S = 1$ indicating perfect similarity of the species compared.

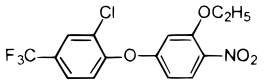
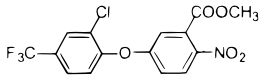
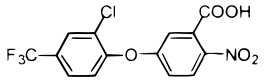
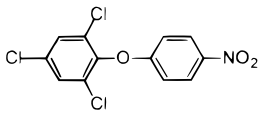
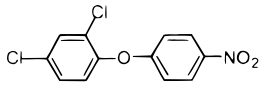
In order to calculate the index S between each cyclic imide and the protogen model, the three carbon atoms (1, 2 and 3 according to the numbering shown for compound **2** in Table 1) of cyclic imides were superimposed onto a nitrogen atom (N 24) and two carbon atoms (C 23, C 26) of the protogen model, respectively, using the least-square fitting method. (see Table 1). The shape similarity indexes between diphenyl ethers and protogen model are shown in Table 2.

By examining the superimposition patterns, cyclic imides were found to match with the C and D rings of protogen, and the values of the index S were in the range of 0.62–0.85. On the other hand, diphenyl ethers matched better with the B and C rings (S_{BC} were in the range of 0.80–0.86) than C and D rings of protogen (S_{CD} were in the range of 0.63–0.68). The 2-ethoxycarbonyl group at the C ring matched with the *meta* substituent at the benzene ring of

Table 1. Protox inhibition and shape similarity index of cyclic imides

No	*Compound*	*pI_{50}(Protox)*[a]	*S_{CD}*[b]
1		4.41	0.62
2		5.80	0.75
3		7.60	0.80
4		9.40	0.85
16		9.05	0.83
21		6.96	0.74
23		8.29	0.79
26		8.57	0.81

[a] pI_{50}(Protox) = −log [molar I_{50} of protox isolated from corn].
[b] Shape similarity index between diphenyl ethers and C and D ring of protogen.

No	Structure	pI_{50}(Protox)[a]	S_{BC}[b]	S_{CD}[c]
27		8.89	0.80	0.63
28		8.66	0.83	0.64
29		6.70	0.85	0.65
30		7.82	0.85	0.67
31		7.72	0.86	0.68

[a] pI_{50}(Protox) = −log [molar I_{50} of protox isolated from corn].
[b] Shape similarity index between diphenyl ethers and B and C ring of protogen.
[c] Shape similarity index between diphenyl ethers and C and D ring of protogen.

Table 2. Protox inhibition and shape similarity index of diphenyl ethers

Atoms	Degree	Atoms	Degree
A-B rings		**C-D rings**	
C1-C6-C11-C12	−123.60	N25-C24-C21-C20	47.30
N7-C6-C11-C12	53.40	C26-C24-C21-C20	−132.90
C6-C11-C12-N13	60.40	C24-C21-C20-N17	43.00
C6-C11-C12-C15	−116.70	C24-C21-C20-C19	−139.20
B-C rings		**D-A rings**	
N13-C14-C22-C23	−72.40	N17-C10-C9-C8	−47.40
C16-C14-C22-C23	106.30	C18-C10-C9-C8	133.00
C14-C22-C23-N25	−34.50	C10-C9-C8-N7	−53.80
C14-C22-C23-C27	147.40	C10-C9-C8-C4	129.10

Table 3. Torsion angles in the most stable conformation of the protoporphyrinogen IX

cyclic imides. This superimposability is one of the very important factors in mimicking the substrate. There was a significant correlation between the protox-inhibiting activity and the similarity index of cyclic imides as shown by eqn (2), in which n, r, s and F represent the number of data, the correlation coefficient, the standard deviation and the ratio of regression and residual variances, respectively, and the figures in parentheses are within the 95% confidence interval.

$$pI_{50}(\text{Protox}) = 20.3(\pm 3.31)S_{CD} - 8.10$$
$$(n = 26,\ r = 0.93,\ s = 0.46,\ F_{1,24} = 160.5) \quad (2)$$

These results indicate that structural similarity is a very important factor in the recognition of protox between inhibitors and the substrate substructure. These comparative experiments show that cyclic imides and diphenyl ethers inhibit the protox, but the binding sites for both herbicide classes in the protex enzyme are different.[3]

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Structure and fungicidal activities of methoxyiminophenylacetamide derivatives

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Abstract: Methoxyiminoacetamides derived from ring-cleaved isoxazole compounds are active against economically important fungal diseases of many crops. Our approach, based upon biorational design, resulted in the production of methoxyiminophenylacetamide derivatives similar in their chemical

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